(c) detecting the presence or absence of said labeled complex, thereby determining the presence or absence of IgA anti-OmpC antibodies,

where the presence of said IgA anti-OmpC antibodies in said subject indicates that said subject has Crohn's disease.

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REMARKS

Claims 1 to 11 are pending, with claims 8 to 11 having been withdrawn from consideration. Claim 3 has been amended herein. Thus, claims 1 to 7 are presently under examination.

Regarding the amendments

Claim 3 has been amended to independent form. This amendment to claim 3 adds no new matter.

Attached as Appendix A is a marked up version of the claim amendment in which text to be deleted is enclosed in brackets and text to be added is underlined.

As set forth above, the claim amendment does not add new matter. Therefore, Applicants respectfully request that the Examiner enter the amendment.

Regarding the restriction requirement

The Office Action indicates that examination of claims 8 to 11 would require a search different from that performed for claims 1 to 7. Applicants submit that a search of elected claims 1 to 7 would be coextensive with a search of claims 8 to 11. In this regard, both elected claims 1 to 7 and claims 8 to 11 involve determining the presence of anti-OmpC antibodies in a sample from a subject suspected of having inflammatory bowel disease. Thus, a search of the methods of claims 1 to 7 will encompass literature that describes determining the presence of IgA anti-OmpC antibodies, whether such literature describes testing only for IgA anti-OmpC antibodies, or testing for IgA anti-OmpC antibodies together with other substances. It is therefore clear that literature relevant to claims 8 to 11, which involve determining the presence or absence of IgA anti-OmpC antibodies as well as other markers, would be identified by a search of claims 1 to 7. Although the Examiner may need to review the identified references with respect to claim elements recited in claims 8 to 11, Applicants submit that such a review would not impose a serious burden on the Examiner. In the absence of a serious burden, restriction is improper. Therefore, Applicants respectfully request that the Examiner remove the restriction requirement and search and examine claims 8 to 11 together with elected claims 1 to 7.

Regarding the enablement rejection of claims 1 to 7 under 35 U.S.C. § 112, first paragraph

The objection to the specification and corresponding rejection of claims 1 to 7 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, respectfully are traversed.

Regarding IgA anti-OmpC antibodies as a sole diagnostic marker

The Office Action acknowledges that the specification enables claims to methods for diagnosing Crohn's disease that involve determining the presence of anti-OmpC antibodies together with anti-Saccharomyces cerevisiae (ASCA) antibodies, anti-I-2 antibodies (I-2) and anti-perinuclear anti-neutrophil antibodies (pANCA). However, it is alleged that the specification fails to enable a method of diagnosing Crohn's disease by determining the presence of IgA anti-OmpC antibodies alone. In particular, the Office Action states:

> The fact that the claimed method appears to work in identifying 55% of patients having CD is not sufficient to enable the breadth of the claimed method for using IgA OmpC as a sole diagnostic marker of CD in patients. The specification does not establish a direct correlation which would lead the skilled artisan to say that if the claimed method works in 55% of CD patients, then it should work in all patients having CD, to enable the breadth of the claimed method (page 7, second paragraph).

Applicants respectfully disagree with the assertion in the Office Action that the claimed methods must work in all patients having Crohn's disease in order to enable the full scope of the claims. In this regard, it is well established that no diagnostic method need be 100% sensitive to be useful and valuable. This point is substantiated by the fact that few, if any, diagnostic tests used in the world today meet the level of 100% sensitivity. Rather, various well-known diagnostic tests fall well below 100% sensitivity and yet are considered useful and valuable. As an example of acceptable standards for diagnostic testing, Applicants submit a bulletin prepared by Bayer Diagnostics describing the historical use of prostate specific antigen (PSA) in prostate cancer diagnostic methods (Exhibit 1). The bulletin indicates that determination of PSA at the traditional level of 4.0 ng/ml is about 75% sensitive and about 40% specific (see paragraph 6 under heading "Prostate Specific Antigen (PSA) Background Information"). In spite of less than 100% sensitivity or specificity, the bulletin states that since the 1980's this test has "profoundly impacted the way in which CaP [prostate cancer] is treated." In sum, a diagnostic method that permits detection of a disease in fewer than 100% of patients having the disease is clearly valuable and can have an important impact on patient care.

Moreover, as pointed out in the Office Action, the specification exemplifies identifying patients having Crohn's disease by determining the presence of IgA anti-OmpC antibodies, IgA anti-I-2 antibodies, and anti-pANCA antibodies individually. Specifically, these tests were used to positively diagnose 56%,

52% and 25%, respectively, of patients having Crohn's disease in a sample patient cohort (see page 7, Table 2). In addition, as shown in Figure 4 of the specification, determining the presence of IgA anti-OmpC antibodies in normal patients indicated that only one of 26 patients had false positive results. Thus, the method was 96% specific in the population tested, which surpasses the specificity of the above-mentioned well-accepted PSA diagnostic. In view of these patient testing results, Applicants submit that, even if only 1 in 4 patients having Crohn's disease were identified, the use of the claimed methods would eliminate for many patients the need for subsequent painful, costly and invasive visual examination of the bowel. Further, a positive diagnosis of Crohn's disease in any percentage of patients is valuable for differentiating between inflammatory bowel diseases and determining a proper course of treatment for a given subject. Thus, the claimed diagnostic methods need not be 100% sensitive. Furthermore, one skilled in the art would have been able to practice the invention by determining the presence of IgA OmpC antibodies alone or in combination with one or more other markers without undue experimentation. For these reasons, Applicants request that the Examiner remove this ground for rejection of claims 1 to 7 as allegedly lacking enablement.

Regarding reactive fragments

The Office Action acknowledges that claims reciting the use of OmpC antigen amino acid sequence SEQ ID NO:1 are enabled by the specification, but asserts that claims that recite reactive fragments of OmpC antigen lack enablement. The Office

Action also acknowledges, in reference to Wands factors used for considering whether claims are overly broad, that the state of the diagnostic art is high (see Office Action, page 5, third paragraph).

Applicants submit that, in view of the high level of skill in the diagnostic art as acknowledged by the Examiner, the skilled artisan possessed the ability to perform the routine work of making a reactive fragment of an OmpC antigen and confirming the ability of the reactive fragment to form a complex with IgA anti-OmpC antibodies. Such laboratory work would have been routine to one skilled in the art in view of guidance provided in the specification and would not have required undue experimentation.

In addition, the specification provides an amino acid sequence corresponding to OmpC (SEQ ID NO:1), which would have been used as a starting material for identifying an OmpC antigen reactive fragment (see Figure 5). As guidance for the skilled person, the specification provides and teaches several methods for identifying a reactive fragment of an OmpC antigen, as well as for confirming immunoreactivity of a reactive fragment. Using these methods, one skilled in the art would have been able to produce a variety of OmpC antigen reactive fragments without undue experimentation. For example, only routine work would have been required to screen a panel of peptides spanning the entire sequence of an OmpC antigen, such as SEQ ID NO:1, or to prepare fragments having a deletion or substitution of one or more amino acids as compared to SEQ ID NO:1 (page 28, lines 4-7; page 15,

line 23, to page 16, line 2). As disclosed in the specification, such a peptide panel can be a collection of 15-mer peptides spanning the sequence of OmpC antigen (SEQ ID NO:1), each overlapping by three or five residue shifts, and can be prepared using Mimotope cleavable pin technology (page 28, lines 7-13). In view of the high level of skill in the diagnostic art and the guidance provided in the specification, only routine work would have been required to obtain a variety of OmpC antigen fragments.

Having prepared an OmpC antigen fragment, one skilled in the art would have readily confirmed that the fragment forms a complex with IgA anti-OmpC antibodies using routine methods. In this regard, the specification teaches procedures for detecting formation of a complex between a fragment of an OmpC antigen, such as a fragment of SEQ ID NO:1, and IgA anti-OmpC antibodies. For example, the specification describes routine ELISA assay in Example II, in which plates are coated with recombinant antigen and complex detected using an alkaline phosphatase-labeled antibody. Using the guidance provided in the specification, undue experimentation would not have been required to practice the invention with any of a variety of OmpC antigen reactive fragments.

In summary, considering that the specification discloses how to prepare and confirm reactivity of a reactive fragment of an OmpC antigen, and further provides as starting material an OmpC amino acid sequence from which a reactive fragments would have been made, Applicants submit that one skilled in the art would have made and used a variety of OmpC

antigen reactive fragments without undue experimentation. Accordingly, Applicants submit that the full scope of the methods of the invention that employ a reactive fragment of OmpC antigen is enabled by the specification, and request that the Examiner remove this ground for rejecting claims 1 to 7 as allegedly lacking enablement.

Regarding the written description rejection under 35 U.S.C. § 112, first paragraph

The objection to the specification and corresponding rejection of claims 1 to 7 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description are respectfully traversed.

The Office Action alleges that the specification fails to provide adequate description for use of reactive fragments in the claimed methods. In particular, the Office Action argues that:

> representative species of fragments and analogs are not described with respect to structure, physical or chemical characteristics, function correlated with structure or a combination of each of the aforementioned, sufficient to establish that the applicant had possession of the claimed reactive fragments and analogs (page 6, first complete sentence).

Applicants submit that the specification provides sufficient description of reactive fragments of OmpC antigen to establish that Applicants had possession of the claimed

invention. With respect to structure and physical or chemical characteristics of a reactive fragment of an OmpC antigen, the specification provides an exemplary amino acid sequence of OmpC antigen (SEQ ID NO:1; see Figure 5). One skilled in the art would have recognized that Applicant had possession of a variety of reactive fragments of OmpC antigen that are substantially similar to a portion of SEQ ID NO:1. With respect to function correlated with structure, the specification teaches that a reactive fragment of an OmpC antigen possesses the function of having reactivity with IgA antibodies in sera of Crohn's disease patients (page 13, lines 13-23). One skilled in the art would have recognized that this function can be readily confirmed for any reactive fragment of an OmpC antigen using routine methods, such as the ELISA described above. Thus, the description of both structural and functional characteristics of reactive fragments of an OmpC antigen in the specification would have indicated to one skilled in the art that Applicants had possession of the claimed invention at the time the subject application was filed. For these reasons, Applicants request that the Examiner remove this rejection of claims 1 to 7 as allegedly lacking written description in the specification.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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APPENDIX A

3. (Amended) [The method of claim 2,] A method of diagnosing Crohn's disease in a subject, comprising the steps of:

(a) contacting a sample from a subject suspected of having inflammatory bowel disease with an OmpC antigen, or reactive fragment thereof, under conditions suitable to form a complex of the OmpC antigen, or reactive fragment thereof, and IgA antibody to the OmpC antigen, wherein said OmpC antigen comprises substantially the amino acid sequence of SEQ ID NO:1;

(b) contacting said complex with a labeled anti-IgA antibody to form a labeled complex; and

(c) detecting the presence or absence of said labeled complex, thereby determining the presence or absence of IgA anti-OmpC antibodies,

where the presence of said IgA anti-OmpC antibodies in said subject indicates that said subject has Crohn's disease.